'Dynamic' Starling mechanism: effects of ageing and physical fitness on ventricular–arterial coupling

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Cardiovascular diseases increase with advancing age, associated with left ventricular and arterial stiffening in humans. In contrast, daily exercise training prevents and/or improves both ventricular and arterial stiffening with ageing. We propose a new approach to quantify the dynamics of the Starling mechanism, namely the beat-to-beat modulation of stroke volume (SV) caused by beat-to-beat alterations in left ventricular filling, which we propose reflects the complex interaction between ventricular and arterial stiffness. We hypothesized that the dynamic Starling mechanism would be impaired with ageing, and that this impairment would be prevented and restored by daily exercise training. Two different approaches were employed: (1) a cross-sectional study to assess the effects of ageing and life-long exercise training; and (2) a longitudinal study to assess the effects of one-year endurance training in the elderly. Spectral transfer function gain between beat-to-beat changes in left ventricular end-diastolic pressure and SV was used as an index of the dynamic Starling mechanism. Gain was significantly lower in the sedentary elderly (70 ± 3 years) than in both young individuals (27 ± 6 years) and Masters athletes (68 ± 3 years), and it was significantly lower in Masters athletes than in young controls (elderly: 0.37 ± 0.11; Masters athletes: 0.96 ± 0.55; young: 1.52 ± 0.42 ml m^{-2} mmHg^{-1}, mean $\pm$ S.D.). Gain increased by 65% after one-year exercise training in the elderly, although the response was quite variable ($P = 0.108$). These findings suggest that the dynamic Starling mechanism is impaired with human ageing possibly due to ventricular–arterial stiffening. Life-long daily exercise training may minimize this impairment, although the effect may be limited particularly when started later in life.

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Ventricular–arterial stiffness, ageing and physical activity

Cardiovascular diseases increase with advancing age and are associated with ventricular and arterial stiffening in humans (Lakatta, 2003; Lakatta & Levy, 2003). In contrast, life-long endurance training preserves myocardial compliance (Arbab-Zadeh *et al.* 2004); moreover daily exercise training prevents and/or improves central arterial stiffening with human ageing (Vaitkevicius *et al.* 1993; Tanaka *et al.* 2000; Seals, 2003). The heart typically adapts with concentric hypertrophy to confront higher afterload produced by arterial stiffening, resulting in left ventricular systolic and diastolic stiffening (Kass, 2005). This adaptation in turn increases the mechanical stresses imposed on the arteries themselves, resulting in stiffer arteries. Endurance exercise training thus may intercede on this vicious cycle of cardiovascular stiffening by improving ventricular–arterial coupling. Indeed, recent studies demonstrated a strong relationship between arterial stiffness and left ventricular geometry (Roman *et al.* 2000; Gates *et al.* 2003).

Dynamic Starling mechanism

The quantification of the intrabeat dynamic aortic pressure–flow relationship and/or static left ventricular pressure–volume relationship has been used to evaluate ventricular and/or arterial stiffening with ageing or cardiovascular diseases (Kelly *et al.* 1992; Chen *et al.* 1998; Arbab-Zadeh *et al.* 2004; Zile *et al.* 2004; Mazzaro *et al.* 2005; Segers *et al.* 2007). However, there are few studies which focus on beat-to-beat dynamic ventricular–arterial coupling.

Previous work using left ventricular time-varying pressure–volume loops has demonstrated that the left ventricular end-systolic pressure–volume relationship

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(ESPVR) represents left ventricular end-*systolic* elastance, reflecting arterial stiffness and myocardial contractility (Kass & Maughan, 1988; Senzaki *et al.* 1996) (Fig. 1). On the other hand, the left ventricular end-*diastolic* pressure–volume relationship (EDPVR) is determined by left ventricular diastolic stiffness and left ventricular mechanical properties (Kass *et al.* 1990; Arbab-Zadeh *et al.* 2004) (Fig. 1). In this study, we propose a novel index to quantify the dynamic Starling mechanism, by which we mean the beat-to-beat relationship between LVEDP and SV as modified by respiratory-induced alterations in intrathoracic pressure. Conceptually, this index can be explained by changes in both EDPVR and ESPVR as illustrated in Fig. 1: first, a steeper slope of EDPVR results in smaller changes of LVEDV at any given unit change of LVEDP; second, a steeper slope of ESPVR results in smaller changes of SV at any given unit change of LVEDV because variability in stroke work caused by changes in preload volume is translated more into blood pressure changes than into aortic flow and SV. In other words, stiffer arteries reduce SV changes for any given unit change in LV preload. Therefore, either ventricular diastolic or systolic stiffness may reduce changes in SV against unit changes in LVEDP. It is thus quite likely that this dynamic index of ventricular–arterial coupling reflects the complicated interaction between left ventricular and arterial stiffness, suggesting a time-varying model of ventricular–arterial coupling (Fig. 1). Indeed, recent findings from this laboratory support these considerations (Shibata *et al.* 2006*a*,*b*). Therefore, this approach to quantifying the dynamic Starling mechanism may provide a unique and unified insight as to how ageing and/or exercise training modify ventricular–arterial stiffness.

The primary purpose of the present study was to assess how human ageing and/or regular exercise training modulate beat-to-beat and breath-to-breath dynamic ventricular–arterial coupling. To address this purpose, we applied two different approaches: (1) a cross-sectional study to assess the effects of ageing and life-long exercise training on the dynamic Starling mechanism, and (2) a longitudinal study to assess the effects of one-year endurance exercise training in the elderly (> 65 years old). We hypothesized that the dynamic Starling mechanism would be impaired with ageing, and that the impairment of the dynamic Starling mechanism with ageing would be prevented and restored by daily exercise training in the elderly.

Methods

Protocol I: cross-sectional study

Twelve healthy sedentary elderly adults (age: > 65 years), and 11 Masters athletes (age: > 65 years) were recruited for the cross-sectional study. Twelve healthy sedentary young individuals (age: < 40 years) from previous studies in our laboratory were used as young controls.

Subjects were excluded if one of following was present: (1) physiologically significant obstructive coronary artery disease as determined by provocable ischaemia during exercise electrocardiogram and echocardiogram, (2) significant valvular heart disease by

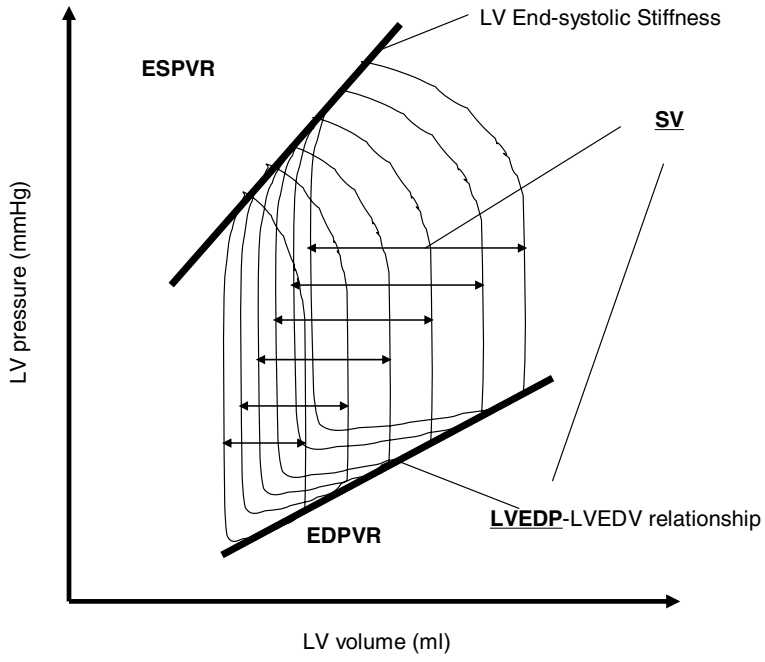

Figure 1
This figure represents a physiological explanation for the dynamic Starling mechanism, the beat-to-beat dynamic relationship between left ventricular end-diastolic pressure (LVEDP) and stroke volume (SV). Each loop represents the left ventricular pressure–volume relationship during one cardiac cycle. The end-systolic pressure–volume relationship (ESPVR) reflects left ventricular (LV) end-systolic stiffness, while the end-diastolic pressure–volume relationship (EDPVR, LVEDP–LVEDV relationship) reflects LV end-diastolic stiffness. The beat-to-beat dynamic relationship between LVEDP and SV is determined by both ESPVR and EDPVR.

echocardiogram, (3) renal dysfunction (serum creatinine $> 2.0\,\mathrm{mg\,dl^{-1}}$), (4) previous coronary artery bypass surgery, (5) arrhythmias such as atrial fibrillation/flutter or left bundle branch block, (6) lung disease (pulmonary HTN or COPD), (7) untreated thyroid disorders, (8) warfarin use, (9) mean daytime blood pressure greater than 140/90 mmHg, (10) right or left ventricular hypertrophy (by ECG or echocardiogram only in sedentary subjects), (11) regular cigarette smoking within the previous 10 years, (12) body mass index $> 30\,\mathrm{kg\,m^{-2}}$, and (13) cardiovascular medication.

Sedentary subjects were excluded if they engaged in endurance exercise for more than 30 min per session, 3 times per week (Levine *et al.* 1991). Masters athletes were recruited as previously reported (Arbab-Zadeh *et al.* 2004). They had participated in regular endurance competitions for 23 ± 8 years (mean $\pm$ S.D.), with a weekly running mileage of 32 ± 10 miles or equivalent swimming or cycling. Both static left ventricular chamber compliance and Doppler measures of left ventricular relaxation have been previously reported on these volunteers (Arbab-Zadeh *et al.* 2004; Prasad *et al.* 2007).

The experimental procedures were explained to all subjects with written informed consent obtained as approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and the Presbyterian Hospital. All procedures conformed to the standards set by the *Declaration of Helsinki*.

Peak oxygen uptake

A modified Astrand–Saltin incremental treadmill protocol was used to determine peak exercise capacity as previously described in all subjects (Balke *et al.* 1965; Okazaki *et al.* 2005; Hawkins *et al.* 2007). Briefly, subjects walked or jogged at a constant speed, which was determined based on the individual subject's fitness to achieve a peak work rate at 10–12 min; the gradient was subsequently increased by 2% every 2 min until exhaustion. Expired gas was collected in Douglas bags in the second minute of each of the final three stages (as predicted from screening test data), with consecutive 45 s collections when the subject was nearing maximal effort. Gas volume was measured with a Tissot spirometer and gas fractions with a mass spectrometer. Heart rate (HR) was monitored continuously via ECG. Maximal oxygen uptake ($\dot{V}_{O_2,max}$) was defined as the highest oxygen uptake measured from a Douglas bag collected for at least 40 s. $\dot{V}_{O_2,max}$ was corrected by body mass and lean body mass calculated from underwater weighing.

Dynamic and static haemodynamics

Measurements. In order to quantify beat-to-beat changes in left ventricular preload pressure and stroke volume, continuous measurements of pulmonary artery and finger artery pressures were made. A 6-F balloon-tipped, fluid-filled catheter (Swan-Ganz, Baxter) was placed through an antecubital vein into the pulmonary artery under fluoroscopic guidance. Pulmonary artery pressure (PAP) was referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero reading set at 5 cm below the sternal angle. Beat-to-beat pulmonary artery diastolic pressure (PAD) was used as an index of beat-to-beat left ventricular end-diastolic pressure to avoid the risks of prolonged balloon inflation (Fisher *et al.* 1975). Photoplethysmography (Portapres, Ohmeda) was used to continuously measure finger arterial blood pressure (ABP) with the height correction transducer positioned at 5 cm below the sternal angle. Beat-to-beat changes in stroke volume were calculated from the finger arterial pressure waveform using pulse contour analysis with the Modelflow method (BeatScope) (Wesseling *et al.* 1993; van Lieshout *et al.* 2003; Bogert & van Lieshout, 2005). In addition, respiratory excursions were monitored continuously via a piezoelectric transducer (Pneumotrace, Morro Bay).

For static haemodynamics, the mean pulmonary capillary wedge pressure (PCWP) was determined visually at end-expiration. Three-lead ECG (Philips Agilent Monitor) was used to measure heart rate. Brachial arterial pressures were measured by electrosphygmomanometry (Suntech). Cardiac output was measured with the C_2H_2 rebreathing method as previously described (McGuire *et al.* 2001).

Experimental protocol. All experiments were performed in the morning at least 2 h after a light breakfast in a quiet environmentally controlled laboratory with an ambient temperature of 25°C. The subjects were asked to refrain from heavy exercise and caffeinated or alcoholic beverages for at least 24 h before the tests. All medications were stopped at least 24 h prior to an experiment. Measurements of cardiac output and brachial blood pressures (electrosphygmomanometry) were made every 5 min in the supine position with ECG monitoring until subject haemodynamics became stable. Haemodynamic stability was confirmed by three sequential cardiac outputs within 10% of each other, and then SV was calculated with cardiac output and each coincident HR. The average of 2–3 sequential SVs was used as baseline SV. After confirmation of haemodynamic stability, subjects were asked to breathe at a controlled breathing frequency (0.2 Hz, 12 breaths $\mathrm{min^{-1}}$) for 8 min by following a moving cursor displayed on a computer. We selected 0.2 Hz for respiratory frequency since it was confirmed by our previous study that dynamic ventricular–arterial coupling can be estimated most reliably at around 0.2 Hz (Shibata *et al.* 2006*b*). Following a 2 min adjustment period, the last 6 min of data were used for data analysis.

Data analysis. PAP and ABP waveforms were digitized through 16-bit analog to digital conversion, stored in a laboratory computer at 200 Hz, and processed with a custom-designed program for beat-to-beat PAD detection (Biopac). Beat-to-beat each Modelflow SV computed from finger arterial pressure waveform was calibrated by a constant, the ratio of mean Modelflow SV to baseline SV with C_2H_2 rebreathing method, according to the method previously validated (Wesseling *et al.* 1993; van Lieshout *et al.* 2003; Bogert & van Lieshout, 2005). SV index (SVi), SV divided by body surface area (Mosteller's equation) (Verbraecken *et al.* 2006), was used in order to minimize the effects of difference in body size between individuals.

For spectral transfer function analysis, beat-to-beat PAD and SVi were linearly interpolated and then resampled at 2 Hz for spectral analysis. The time series of PAD and SVi were first detrended with third-order polynomial fitting and then subdivided into 256 point segments with 50% overlap for spectral estimation. This process resulted in five segments of data over the 6 min period recordings. Fast Fourier transforms were implemented with each Hanning-windowed data segment and then averaged to calculate auto-spectra $[S_{\mathrm{PAD\ PAD}}(f)]$, $[S_{\mathrm{SVi\ SVi}}(f)]$, and cross-spectra $[S_{\mathrm{PAD\ SVi}}(f)]$ for PAD and SVi variability, respectively. The minimal spectral resolution for these estimates is 0.0078 Hz. Transfer function $[H(f)]$ between PAD and SVi variabilities was obtained with the following equations:

$$H(f) = S_{\mathrm{PAD\ SVi}}(f)/S_{\mathrm{PAD\ PAD}}(f)$$

Transfer function gain and phase were derived from the real part $[H_{\mathrm{R}}(f)]$ and the imaginary part $[H_{\mathrm{I}}(f)]$ of the complex transfer function as:

$$|\mathrm{Gain}(f)| = \left\{[H_{\mathrm{R}}(f)]^2 + [H_{\mathrm{I}}(f)]^2\right\}^{1/2}$$

$$\mathrm{Phase}(f) = \tan^{-1}[H_{\mathrm{I}}(f)/H_{\mathrm{R}}(f)]$$

The transfer function phase ranges from $-\pi$ to $+\pi$, and yields a negative value when changes in the input precede changes in the output at each frequency. Phase zero indicates complete synchrony between the input and output. The transfer function gain, similar conceptually to the slope of a linear regression, reflects changes in the output against a unit change of the input at each frequency. Thus, the gain between PAD and SVi was used as an index of the dynamic Starling mechanism which reflects a function of beat-to-beat modulations of stroke volume against changes in left ventricular preload pressures.

Coherence function was derived from $[S_{\mathrm{PAD\ PAD}}(f)]$, $[S_{\mathrm{SVi\ SVi}}(f)]$, and $[S_{\mathrm{PAD\ SVi}}(f)]$ as:

$$\mathrm{Coherence} = [S_{\mathrm{PAD\ SVi}}(f)]^2/[S_{\mathrm{PAD\ PAD}}(f)S_{\mathrm{SVi\ SVi}}(f)]$$

The reliability of linear transfer function estimation was evaluated by the estimates of coherence function which ranges between 0 and 1. A value of unity indicates a perfectly linear relationship between the input and output at each frequency, similar conceptually to the r^2 value of a linear regression.

The spectral power of the input variable (PAD) and output variable (SVi) of the dynamic Starling mechanism was calculated in the respiratory frequency range (0.18–0.22 Hz) by integrating the corresponding auto-spectra (Saul *et al.* 1991; Shibata *et al.* 2006*b*). Mean values of transfer function gain and phase, and coherence function were calculated in the respiratory frequency range (0.18–0.22 Hz) and averaged for all subjects in each group to estimate the dynamic Starling mechanism (Saul *et al.* 1991; Shibata *et al.* 2006*b*).

Protocol II: exercise intervention

Nine of the 12 sedentary elderly adults underwent exercise training in accordance with a training programme prescribed individually for each subject over one year as previously described (Okazaki *et al.* 2005). Briefly, on the basis of HR measured at maximal steady state estimated from ventilatory threshold and maximal HR during a maximal exercise test performed before and every 3 months of training, training intensity and duration were determined. HR was monitored and measured during every training session, and training stimuli were evaluated by the method of Banister *et al.* (1992). All of the exercise training was supervised regularly by exercise physiologists. Subjects gradually increased their exercise level and finally achieved weekly exercise training up to 4–6 h at the end of one year of training, including long distance, maximal steady state and interval training.

The same measurements for the dynamic Starling mechanism and exercise testing were repeated after one year of exercise training.

Statistical analysis

Numerical data are presented as mean ± S.D. except for the graphics, in which S.E.M. is used. Differences in variables among Masters athletes, the sedentary elderly and young individuals were compared by using one-way ANOVA. Student–Newman–Keuls-corrected *t* test was used for multiple comparisons during *post hoc* testing. Differences in variables between pre and post one-year exercise training were compared by using paired *t* tests. Statistical analysis was performed by computer software (SigmaStat 3.00, SPSS).

Results

Protocol I

Subject characteristics. Table 1 shows the subject characteristics for the cross-sectional study. The sedentary

Table 1. Subject characteristics for cross-sectional study

	Elderly Unfit	Elderly Fit	Young Unfit
Male/Female	6/6	5/6	7/5
Age (years)	70 ± 3‡	68 ± 3‡	27 ± 6
Height (cm)	168 ± 10	170 ± 12	172 ± 7
Weight (kg)	73 ± 11	65 ± 14	70 ± 9
BMI (kg m^{-2})	25.8 ± 2.4*‡	22.1 ± 1.9	23.5 ± 1.8
BSA (m^2)	1.85 ± 0.18	1.74 ± 0.25	1.82 ± 0.15
$\dot{V}_{O_2,max}$ (l min^{-1})	1.62 ± 0.42*‡	2.46 ± 0.68	2.63 ± 0.71
$\dot{V}_{O_2,max}$/BM (ml kg^{-1} min^{-1})	21.9 ± 3.6*‡	38.2 ± 6.2	37.5 ± 7.6
$\dot{V}_{O_2,max}$/LBM (ml kg^{-1} min^{-1})	30.8 ± 5.2*‡	46.9 ± 8.1	49.0 ± 7.0

Values are means ± S.D. Elderly Unfit, the sedentary elderly; Elderly Fit, Masters athletes; Young Unfit, sedentary young individuals; BMI, body mass index; BSA, body surface area; BM, body mass; LBM, lean body mass; *$P < 0.05$ *versus* Elderly Fit; ‡$P < 0.05$ *versus* Young Unfit.

elderly had a slightly higher body mass index (BMI) than both Masters athletes and young individuals, although height, weight, and body surface area (BSA) were similar. The sedentary elderly had a lower $\dot{V}_{O_2,max}$ than both Masters athletes and young individuals while there were no significant differences between Masters athletes and young individuals in $\dot{V}_{O_2,max}$.

Steady-state haemodynamics

The sedentary elderly had higher blood pressures (systolic, diastolic and mean) than young individuals and Masters athletes, while there were no significant differences between Masters athletes and young individuals in blood pressures (Table 2). Pulse pressure was significantly lower in young individuals than in the sedentary elderly and Masters athletes. Masters athletes had lower HR than both the sedentary elderly and young individuals, suggesting the effects of exercise training (Table 2). PCWP and mean PAD were significantly lower in Masters athletes than those of young individuals, but the changes were physiologically very small (only 2.2 and 2.4 mmHg in PCWP and PAD, respectively). SVi as well as SV were significantly lower in the sedentary elderly than both Masters athletes and young individuals.

Dynamic haemodynamics

Representative data of time series of beat-to-beat PAD and SVi from one sedentary elderly subject are shown in Fig. 2*A*. Autospectra of PAD and SVi, and coherence function and transfer function gain and phase between PAD *versus* SVi from the same subject are shown in Fig. 2*B* and *C*. Coherence function was higher than 0.5 in the range from 0.18 to 0.22 Hz, and showed a peak at the respiratory

Table 2. Haemodynamics for cross-sectional study

	Elderly Unfit	Elderly Fit	Young Unfit
HR (beats min^{-1})	67 ± 9*	55 ± 6‡	67 ± 10
SBP (mmHg)	138 ± 15*‡	125 ± 20	114 ± 6
DBP (mmHg)	79 ± 8*‡	69 ± 10	68 ± 6
MBP (mmHg)	98 ± 10*‡	88 ± 13	83 ± 5
PP (mmHg)	59 ± 9‡	56 ± 12‡	46 ± 10
PCWP (mmHg)	11.6 ± 1.9	10.2 ± 1.2‡	12.4 ± 1.6
PAD mean (mmHg)	7.6 ± 2.0‡	7.3 ± 2.0‡	9.7 ± 2.3
PAD S.D. (mmHg)	2.2 ± 0.7*	1.4 ± 0.4	1.9 ± 0.6
SV mean (ml)	73 ± 19*‡	97 ± 22	99 ± 19
SV S.D. (ml)	3 ± 1‡	4 ± 1‡	6 ± 2
SVi mean (ml m^{-2})	40 ± 8*‡	55 ± 7	54 ± 9
SVi S.D. (ml m^{-2})	2 ± 1‡	2 ± 1 ‡	3 ± 1
PSD PAD (mmHg^2)	3.79 ± 2.90*	1.38 ± 0.90	2.59 ± 2.26
PSD SVi (ml m^{-2})^2	0.66 ± 0.53‡	1.47 ± 1.15‡	7.82 ± 10.63
Phase PAD–SVi (rad)	−0.15 ± 0.77	−0.80 ± 0.74	−0.76 ± 0.73
Coh PAD–SVi (units)	0.74 ± 0.09	0.66 ± 0.14	0.76 ± 0.14

Values are means ± S.D. Elderly Unfit, the sedentary elderly; Elderly Fit, Masters athletes; Young Unfit, sedentary young individuals; HR, heart rate; SBP, DBP, MBP and PP, systolic, diastolic, mean and pulse pressures, respectively; PCWP, pulmonary capillary wedge pressure measured at end-expiration; PAD mean, mean of beat-to-beat pulmonary artery diastolic pressure during fixed breathing at 0.2 Hz; PAD S.D., time series standard deviation of PAD; SV mean, mean of beat-to-beat stroke volume; SV S.D., time series standard deviation of SV; SVi mean, mean of beat-to-beat stroke volume index, SVi S.D., time series standard deviation of SVi; PSD PAD, power spectral density of pulmonary artery diastolic pressure at the respiratory frequency; PSD SVi, power spectral density of stroke volume index at the respiratory frequency; Phase PAD–SVi, transfer function phase between PAD and SVi; Coh PAD–SVi, coherence function between PAD and SVi; *$P < 0.05$ *versus* Elderly Fit; ‡$P < 0.05$ *versus* Young Unfit.

frequency of 0.2 Hz, indicating the reliability of transfer function gain and phase calculation at the respiratory frequency (Fig. 2*C*, Table 2). Phase was close to zero at the respiratory frequency, indicating that changes in PAD were closely synchronized with those in SV (Fig. 2*C*, Table 2). Neither coherence nor phase was different between groups (Table 2).

The input variable of the dynamic Starling mechanism, namely spectral power of PAD at the range from 0.18 to 0.22 Hz, was significantly lower in Masters athletes than in the sedentary elderly ($P = 0.037$) (Table 2). The output variable of the dynamic Starling mechanism, namely spectral power of SVi in the range from 0.18 to 0.22 Hz, was significantly higher in young individuals than in both the sedentary elderly ($P = 0.023$) and Masters athletes ($P = 0.021$) (Table 2). The dynamic Starling mechanism, quantified as the transfer function gain between PAD and SVi, was significantly lower in the sedentary elderly than

in both young individual and Masters athletes (Fig. 3). The dynamic Starling mechanism in Masters athletes was significantly lower than that of young individuals (Fig. 3).

Protocol II

Subject characteristics. Table 3 shows the subject characteristics for the longitudinal study. Body weight was decreased after one-year exercise training in the previously sedentary elderly, and consequently BSA and BMI also were decreased. $\dot{V}_{O_2,max}$ was augmented after one-year exercise training, although it remained substantially lower than that of Masters athletes.

Steady-state haemodynamics (Table 4)

HR was decreased after one-year exercise training while blood pressures were not different between pre- and post-training. Mean PAD, SV and SVi were increased after one year of exercise training.

Dynamic haemodynamics

The input variable of the dynamic Starling mechanism, spectral power of PAD, decreased by 49% after one year of exercise training ($P = 0.057$) (Table 4). Neither coherence nor phase was different between pre- and post-training (Table 4). The dynamic Starling mechanism, transfer function gain between PAD and SVi, increased by 65% after one-year exercise training, although the response was quite variable ($P = 0.108$) (Fig. 4).

Discussion

The primary findings in the present study include the following: (1) ventricular–arterial coupling of the dynamic Starling mechanism was impaired with healthy sedentary ageing, (2) life-long daily exercise training minimized

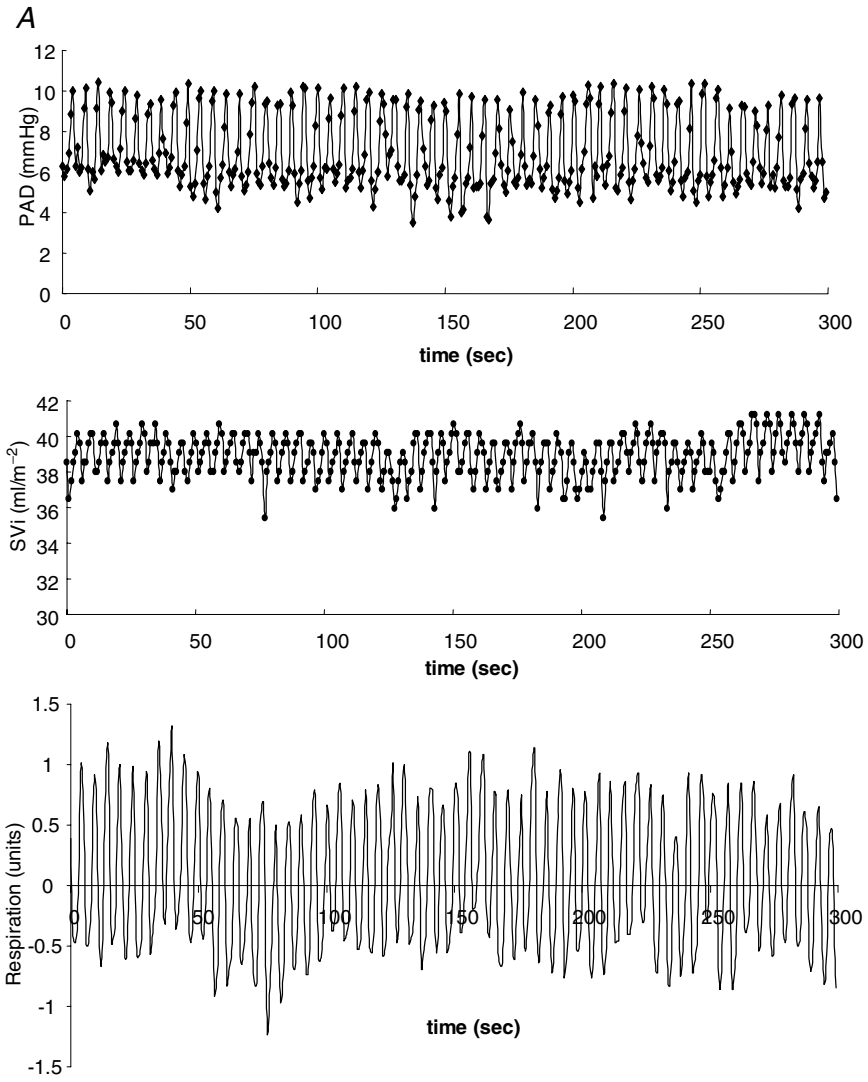

Figure 2*A*
These figures represent the time series of beat-to-beat pulmonary artery diastolic pressure (PAD, upper panel) and stroke volume index (SVi, middle panel) with the respiration trace (lower panel) for one representative subject of the sedentary elderly.

the impairment of the dynamic Starling mechanism with ageing; however (3) unexpectedly, one year of intensive exercise training did not consistently improve the impairment of the dynamic Starling mechanism in the previously sedentary elderly.

Methodological considerations

The coherence function between LVEDP and SVi showed a peak (higher than 0.9) and the phase was almost zero at the respiratory frequency of 0.2 Hz, implying that respiratory changes in left ventricular end-diastolic pressure are closely correlated and synchronized with those in stroke volume presumably via the Starling mechanism. This result suggests that the Starling mechanism is operating dynamically to modulate respiratory changes in preload despite the fact that respiratory changes in LVEDP and SV are also affected by the complex interaction among cardiac filling, intrathoracic pressure, and ventricular interdependence. These findings support the reliability of transfer function gain as an index of the dynamic Starling mechanism.

Dynamic Starling mechanism, ageing and life-long exercise training

Previous studies using these same subjects have shown that the sedentary elderly have a steeper slope of EDPVR than young individuals, indicating an age-related increase in the slope of EDPVR (Arbab-Zadeh *et al.* 2004). The age-related increase in the slope of ESPVR was also reported by other investigators (Chen *et al.* 1998). Moreover, arterial stiffening with ageing in humans has also been demonstrated by other investigators with various approaches such as aortic input impedance (Mazzaro *et al.* 2005), arterial cross-sectional area–pressure relationship (Tanaka *et al.* 2000), aortic pulse wave velocity (Vaitkevicius *et al.* 1993) and arterial pressure contour analysis (McVeigh *et al.* 1999). Therefore, our present findings that the dynamic Starling mechanism was impaired with healthy but sedentary ageing are consistent with previous findings and build upon them by revealing the integrated behaviour of both ventricular and arterial stiffness.

Our finding that Masters athletes have a less impaired dynamic Starling mechanism than the sedentary elderly,

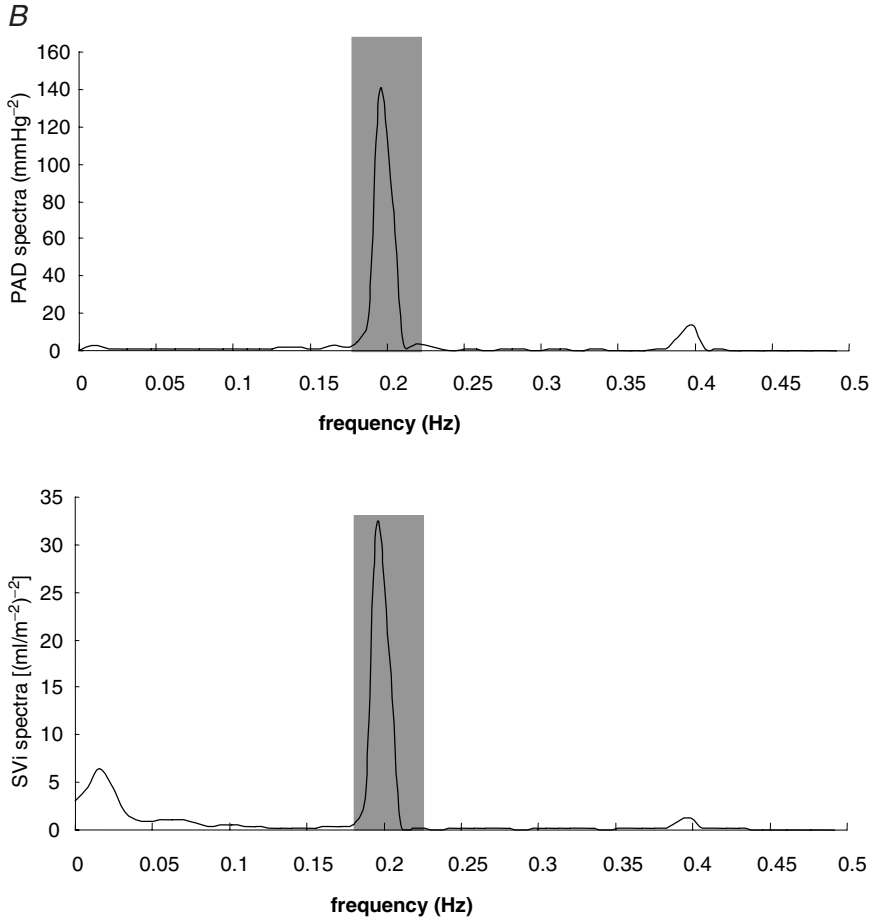

Figure 2*B*
These figures represent autospectra of beat-to-beat pulmonary artery diastolic pressure (PAD spectra, upper panel) and stroke volume index (SVi spectra, lower panel) variabilities for the same representative subject as Fig. 2*A*. Grey bars enhance the respiratory frequency of 0.18–0.22 Hz, where the input and output variable for the dynamic Starling mechanism was quantified.

is also consistent with our previous findings that elite Masters athletes have more compliant left ventricles and lower effective arterial elastance than the sedentary elderly (Arbab-Zadeh *et al.* 2004). Other researchers also showed that Masters athletes have more compliant arteries by using an indirect index of aortic stiffness such as aortic pulse wave velocity or aortic augmentation index (Vaitkevicius *et al.* 1993). Taken together, all of these consistent findings would strongly support our physiological model that the dynamic Starling mechanism reflects time-varying ventricular–arterial stiffness.

Interestingly, we found a small but statistically significant difference in the dynamic Starling mechanism between Masters athletes and sedentary young individuals although our previous report using the same subjects showed that static EDPVR was virtually identical between Masters athletes and young individuals (Arbab-Zadeh *et al.* 2004). This finding suggests that even a high level of life-long exercise training may not completely prevent the impairment of the dynamic Starling mechanism with ageing. Since effective arterial elastance was about 13% higher in Masters athletes than in young individuals, but left ventricular compliance was the same (Arbab-Zadeh *et al.* 2004), this residual difference in the dynamic Starling mechanism might be attributable to the presence of stiffer arteries in Masters athletes than in young individuals.

Longitudinal study (one-year exercise training in the elderly)

The present results from the cross-sectional study suggested that *life-long* exercise training minimizes the impairment of the dynamic Starling mechanism with ageing. One recent study by Tanaka *et al.* showed that daily exercise training improves central arterial compliance with ageing (Tanaka *et al.* 2000). However, unexpectedly,

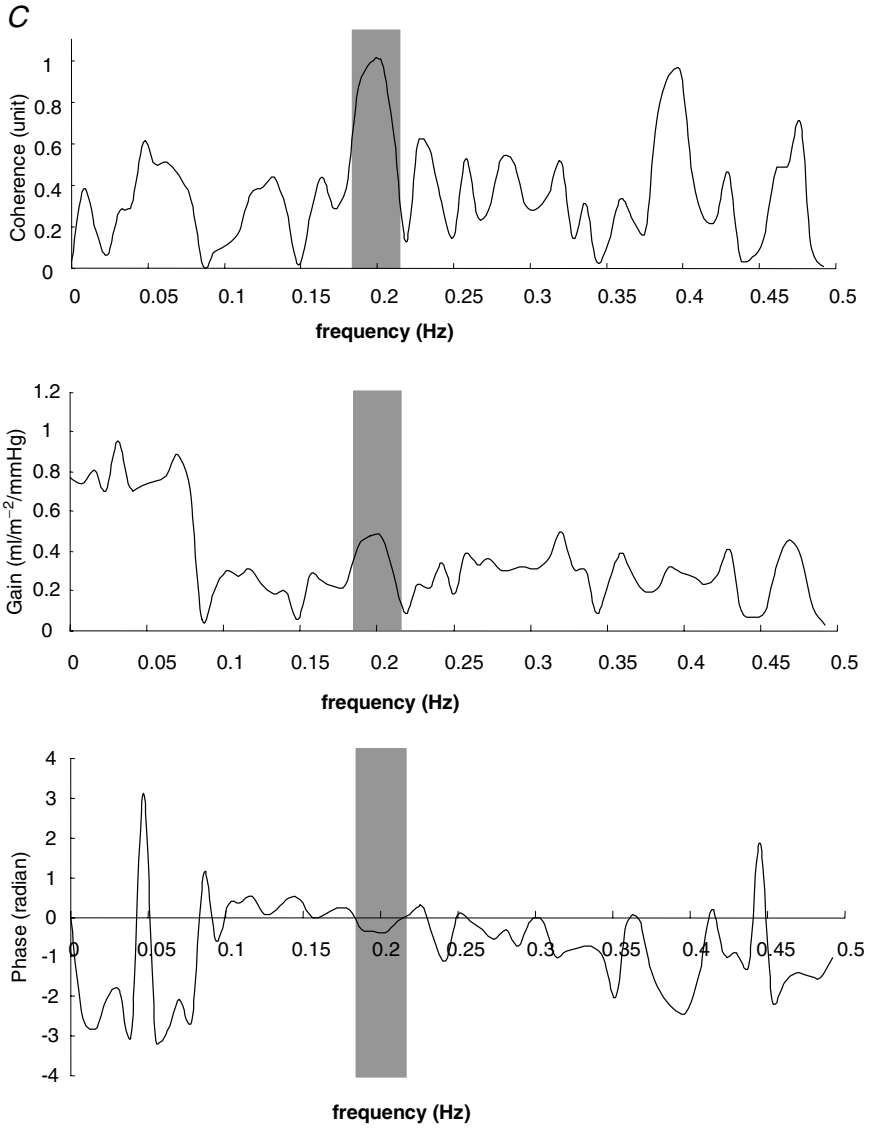

Figure 2*C*
These figures represent the coherence function (upper panel), and transfer function gain (middle panel) and phase (lower panel) between pulmonary artery diastolic pressure (PAD) and stroke volume index (SVi) for the same representative subject as Fig. 2*A*. Grey bars enhance the respiratory frequency of 0.18–0.22 Hz whose coherence was higher than 0.5 where the gain and phase are reliable.

Table 3. Subject characteristics for longitudinal study

	Pre-training	Post-training	*P* value
Male/Female	6/3	—	—
Age (years)	71 ± 3	—	—
Height (cm)	171 ± 9	—	—
Weight (kg)	76 ± 9	72 ± 9†	<0.001
BMI (kg m^{-2})	25.9 ± 1.9	24.7 ± 2.0†	<0.001
BSA (m^2)	1.90 ± 0.16	1.85 ± 0.15†	<0.001
$\dot{V}_{O_2,max}$ (l min^{-1})	1.75 ± 0.39	1.98 ± 0.47†	<0.001
$\dot{V}_{O_2,max}$/BM (ml kg^{-1} min^{-1})	22.8 ± 3.4	27.2 ± 4.3†	<0.001
$\dot{V}_{O_2,max}$/LBM (ml kg^{-1} min^{-1})	32.1 ± 5.2	37.5 ± 6.4†	0.001

Subject characteristics for pre and post one year of exercise training in the previously sedentary elderly. Values are means ± S.D. BMI, body mass index; BSA, body surface area; BM, body mass; LBM, lean body mass; †$P < 0.05$ pre- *versus* post-training.

our longitudinal results indicated that the effects of daily exercise training on the dynamic Starling mechanism in the previously sedentary elderly (age: > 65 years) is, if present, limited. It should also be emphasized, however, that a 65% increase in gain between LVEDP and SVi was observed after one year of exercise training, suggesting potentially significant effects of exercise training on the dynamic Starling mechanism, although it was still substantially lower than that of elite Masters athletes.

The study by Tanaka *et al.* that showed restoration of arterial stiffening with ageing (Tanaka *et al.* 2000) used mainly middle-aged adults whose age (average: 52 years) was much younger than ours (average 71 years). Elite Masters athletes in the present study had participated in regular endurance competitions for an average of 23 years, indicating that they started their exercise training at least from the age of 40–50 years. Thus, these inconsistent findings may be explained by the effects of the age when exercise training started on cardiovascular responses to exercise training.

We can only speculate about the mechanism underlying this discrepancy between life-long *versus* one-year exercise training. Recent findings have shown that permanent cross-linking of collagen in the left ventricle and aorta contributes to ventricular and arterial stiffening with ageing (Aronson, 2003; Zieman *et al.* 2007). Daily exercise training improves glucose–insulin and lipid metabolism, and may reduce blood pressure in young individuals, all of which are considered to be associated with an increase of collagen cross-linking in cardiovascular tissues (Legedz *et al.* 2006; Tomiyama *et al.* 2006). Therefore, it is possible that while accumulation of extracellular cross-linked collagen can be prevented by life-long exercise training, once established, it may be hard to remove or break them by exercise training alone. Another possible explanation is that cardiovascular remodelling is impaired in the elderly. It is apparent that further studies are needed to address these issues.

Study limitations

The most important limitation in the present study is that our physiological parameters were indirectly measured, although these methodologies have been validated and widely accepted in either clinical settings or physiological studies (Wesseling *et al.* 1993; van Lieshout *et al.* 2003; Bogert & van Lieshout, 2005). Direct measurements of beat-to-beat SV and LVEDP, such as left heart catheterization and direct aortic flow measurement, may be needed to confirm these findings, although they are generally too invasive for healthy humans. Non-invasive

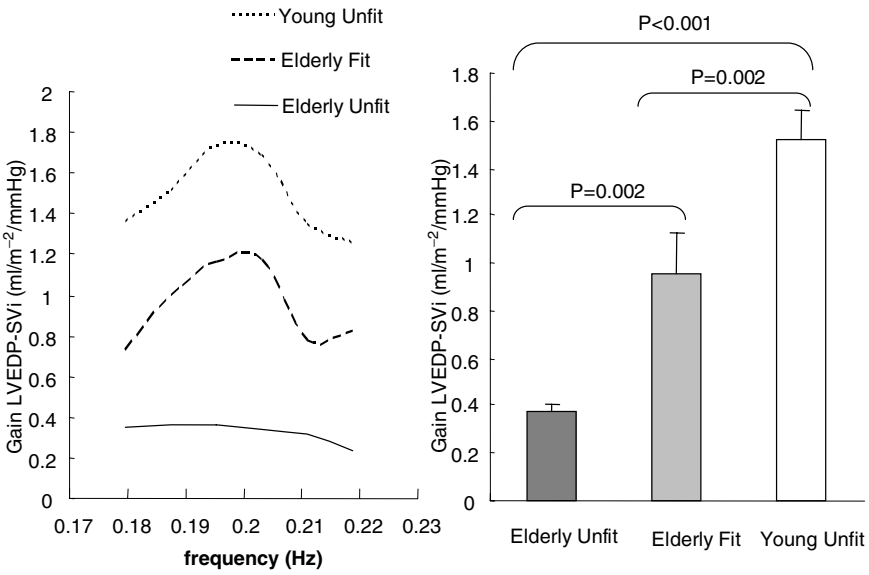

Figure 3
Plots on left panel represent mean transfer function gain between pulmonary artery diastolic pressure (PAD) and stroke volume index (SVi) from all subjects at the respiratory frequency of 0.18–0.22 Hz for the sedentary elderly (Elderly Unfit), Masters athletes (Elderly Fit) and sedentary young individuals (Young Unfit). Right panel represents mean + S.E.M. of individual mean of transfer function gain at the respiratory frequency of 0.18–0.22 Hz for Elderly Unfit, Elderly Fit and Young Unfit.

Table 4. Haemodynamics for longitudinal study

	Pre-training	Post-training	*P* value
HR (beats min^{-1})	66 ± 10	60 ± 12†	0.018
SBP (mmHg)	139 ± 11	139 ± 22	0.957
DBP (mmHg)	79 ± 7	73 ± 4	0.056
MBP (mmHg)	99 ± 8	95 ± 8	0.084
PP (mmHg)	60 ± 6	66 ± 22	0.363
PCWP (mmHg)	11.6 ± 2.2	12.5 ± 2.8	0.262
PAD mean (mmHg)	7.2 ± 1.8	10.5 ± 2.9†	0.011
PAD S.D. (mmHg)	2.3 ± 0.6	1.9 ± 0.5	0.080
SV mean (ml)	78 ± 20	93 ± 21†	0.017
SV S.D. (ml)	3 ± 1	6 ± 3†	0.038
SVi mean (ml m^{-2})	41 ± 9	50 ± 10†	0.009
SVi S.D. (ml m^{-2})	2 ± 1	3 ± 2†	0.036
PSD PAD (mmHg^2)	4.11 ± 2.77	2.10 ± 1.39	0.057
PSD SVi (ml m^{-2})^2	0.71 ± 0.54	0.98 ± 0.92	0.330
Phase PAD–SVi (rad)	−0.22 ± 0.77	−0.74 ± 0.95	0.187
Coh PAD–SVi (units)	0.72 ± 0.10	0.80 ± 0.09	0.101

Haemodynamics for pre and post one year of exercise training in the previously sedentary elderly. Values are means ± S.D. HR, heart rate; SBP, DBP, MBP and PP, systolic, diastolic, mean and pulse pressures, respectively; PCWP, pulmonary capillary wedge pressure measured at end-expiration; PAD mean, mean of beat-to-beat pulmonary artery diastolic pressure during fixed breathing at 0.2 Hz; PAD S.D., time series standard deviation of PAD; SV mean, mean of beat-to-beat stroke volume; SV S.D., time series standard deviation of SV; SVi mean, mean of beat-to-beat stroke volume index, SVi S.D., time series standard deviation of SVi; PSD PAD, power spectral density of pulmonary artery diastolic pressure at the respiratory frequency; PSD SVi, power spectral density of stroke volume index at the respiratory frequency; Phase PAD–SVi, transfer function phase between PAD and SVi; Coh PAD–SVi, coherence function between PAD and SVi; †$P < 0.05$ pre- *versus* post-training.

measurements of aortic blood velocity with the Doppler technique has been used by others to measure beat-to-beat stroke volume changes (Toska & Eriksen, 1993) although breath-by-breath alterations in heart position and Doppler insonation angle might induce artifact in haemodynamics that would appear to be respiratory mediated. For this reason, we chose a well validated method (Modelflow) that is operator independent and not affected by respiration.

Another limitation is the small number of subjects particularly in the longitudinal studies ($n = 9$), which reduces the statistical power of the study. For example, the unexpected results that a significant difference was not observed in the gain between LVEDP *and* SVi (dynamic Starling mechanism) even after one year of exercise training may be explained simply by the small number of subjects recruited. The statistical power was 0.32 with a type I error of 0.05 between pre and post one-year exercise training of dynamic Starling mechanism (difference, 0.26; S.D., 0.43 ml m^{-2} mmHg^{-1}) and 31 subjects would have been needed to achieve a type I error of 0.05 and a power of 0.9. Therefore, it is still unclear whether one year of exercise training has significant effects on the dynamic Starling mechanism in the elderly or not. However, the fact that gain between LVEDP and SVi after one year of exercise training in the elderly was still substantially lower than that of Masters athletes still supports the interpretation that one year of exercise training has a limited capacity to improve the dynamic Starling mechanism in the previously sedentary elderly.

Conclusion

The beat-to-beat dynamic Starling mechanism is impaired with human ageing. Life-long daily exercise training

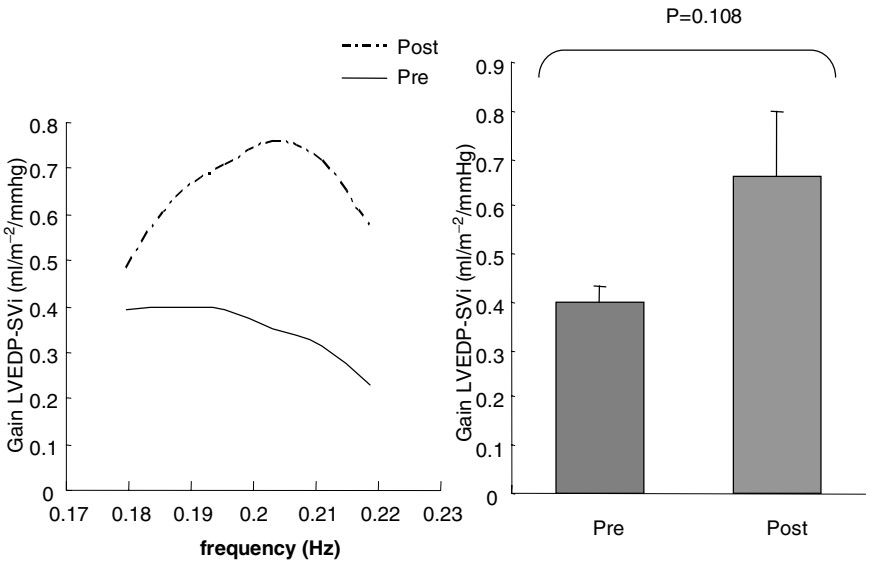

Figure 4
Plots on left panel represent mean transfer function gain between pulmonary artery diastolic pressure (PAD) and stroke volume index (SVi) from all subjects at the respiratory frequency of 0.18–0.22 Hz for pre and post one year of exercise training in the elderly. Right panel represents mean + S.E.M. of individual mean of transfer function gain at the respiratory frequency of 0.18–0.22 Hz for pre and post one year of exercise training.

may prevent the impairment of the dynamic Starling mechanism with ageing, although the effect may be limited when started later in life. These findings are likely to be explained by changes in ventricular–arterial coupling associated with ventricular–arterial stiffening with ageing.

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